II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 2, 18 and 21 have been amended. Claims 1, 8, 17, 19-20, 24 and 39 are canceled. Claims 2-7, 9-16, 18, 21-23 and 25-38 are pending and under examination.

B. Claim Rejections – 35 U.S.C. §103

Claims 2-7, 9-17, 19-23 and 25-38

The Action first rejects claims 2-7, 9-23 and 25-38 as obvious over Harlow in view of Jat, Kano and Kanki. Applicants respectfully traverse the rejection. For reasons discussed below, we contend that there has been no *prima facie* rejection made.

Harlow teaches traditional monoclonal antibody preparation, using hybridoma formation. Thus, Harlow teaches *against* the present invention, which is concerned with monoclonal preparation *without* the need for hybridoma formation. Indeed, Harlow teaches that it is an *absolute requirement* to form hybridomas in order to prepare monoclonal antibodies:

> Figure 6.3 outlines the steps in the production of monoclonal antibodies. Animals are injected with an antigen preparation, and once a good humoral response as appeared in the immunized animal, and appropriate screening procedure is developed. There sera from test bleeds are used to develop and validate the screening procedure. After an appropriate screen has been established, the actual production of the hybridomas can begin. Several days prior to the fusion, animals are boosted with a sample of the antigen. ***For the fusion, antibody-secreting cells are prepared from the immunized animal, mixed with the myeloma cells, and fused.*** After the fusion, cells are diluted in selective medium and plated in multiwell tissue culture dishes. ***Hybridomas are ready to test beginning about 1 week after the fusion.*** Cells from positive wells are grown and then single-cell cloned. Hybridomas production seldom takes less than 2 months from start to finish, and it can take well over a year. ***It is convenient to divide the production of monoclonal antibodies into three stages: (1) immunizing mice, (2) developing the screening procedure, and (3) producing hybridomas.*** Any one of these stages may proceed very quickly, but

> all have inherent problems that should be considered prior to the start of the project, and these areas are discussed separately below.

Harlow, page 148, in the section entitled "Production of Monoclonal Antibodies" (emphasis ours). As can be seen from this excerpt, the only way to prepare monoclonals taught by Harlow is through hybridoma fusion – the reference does not leave open any other possibilities or avenues. Indeed, it states that monoclonal antibody production involves three stages, one of which is "producing hybridomas."

The Examiner implies that Harlow does not necessarily require myeloma fusion/hybridoma formation in order to prepare monoclonal antibodies, but fails to point any specific teaching in Harlow in support of this position. Instead, the Examiner can only direct us to a totally different reference, Kumar (which is not even cited in this obviousness rejection), for the unrelated and irrelevant proposition that Kumar teaches direct immortalization of B-cells. The reference to Kumar is of little relevance to this issue at hand: the question is whether Harlow itself, the primary reference, suggests that any alternative other than myeloma fusion can be used to prepare monoclonals. The Examiner implicitly concedes that it does not.

Jat merely teaches the "immortomouse" that can be used to practice the present invention, but, again, provides no suggestion for using the immortomouse in the preparation of monoclonals. The Examiner inexplicably relies on "a portion" of a statement from Jat concerning the use of fibroblast populations. A reading of the *complete* excerpt, however, shows that Jat is, simply speaking, irrelvant:

> Work with transfected and viral-mediated gene insertion has consistently indicated that techniques developed through the use of fibroblast populations can be transferred readily to other cell systems.

Jat, page 5096, col. 2. When read in total and in context, it is clear that the excerpt says nothing about using antibody-producing cells from transgenic mice to produce monoclonal antibodies – it merely says "other cell systems" without referencing any particular type of cell system. Again, the Examiner has simply failed to point to any language in Jat that would lead one of skill to use Jat's mice for the preparation of immortal, monoclonal-antibody producing cell lines.

Kano, Kanki and Kumar are all very similar references – references that are very clearly not combinable with Harlow and all that very clearly teach away from the present invention. Each of these references concerns the use of an oncogene to prepare transgenic, immortalized B-cell cultures *ex vivo*. In contrast, the present invention does just the opposite: the B-cells that are antigen-primed *already* have the ability to be immortalized! There is no requirement that the B-cell be transformed by an oncogene *in vitro*. This is an important improvement – by avoiding the need to transfect B-cells *ex vivo*, one dramatically improves the overall efficiency, and dramatically reduces the overall complexity, of the process. For example, if the antibody-producing cells are only immortalized by an oncogene *ex vivo*, you now introduce a substantial source of inefficiency, in that only a fairly small percentage of cells would be expected to be immortalized *ex vivo/in vitro* – thus reducing the likelihood of getting one or more desired antibodies. However, in the case of the present invention, all of the antibody-producing cells already include the transforming oncogene, removing this uncertainty and lack of efficiency.

Furthermore, the Examiner has failed to provide a cogent explanation as to how these references are combinable with Harlow. The fact is, they are not combinable with Harlow in that Harlow teaches a different approach – to remove antigenically primed B-cells and immortalize them by a different method, by fusing with a myeloma to form a hybridoma. However, even if these references were to be combined with Harlow, such a combination would lead one of skill

away from the present invention: the only way that one could possibly combine Kano/Kanki/Kumar with Harlow would be to take the "antibody-secreting cells" of Harlow and, instead of forming a hybridoma using a myeloma, to immortalize the antibody-secreting cells *ex vivo* using the technique of Kano/Kanki/Kumar. This is *not* the presently claimed invention!

The present invention is different. The present invention involves the use of mice whose cells already have the ability to be ability to be immortalized without introducing an oncogene *ex vivo*! The only reference that teaches such a mouse is Jat, but, as explained above, Jat provides no suggestion whatsoever to use such mice to prepare monoclonal antibodies, and there are no other references that would suggest such a use of Jat's mice. Indeed, the references relied upon by the Examiner for this purpose, Kano/Kanki/Kumar, teach an altogether different approach.

In this regard, it must be remembered that "[a] person of ordinary skill in the art is ... presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights." *Standard Oil Co. v. American Cyanamid Co.*, 227 USPQ 293, 298 (Fed. Cir. 1985). Thus, one of ordinary skill in the monoclonal antibody art would most certainly follow the "conventional wisdom" of Harlow by using hybridomas to form monoclonal antibodies, or follow the "conventional wisdom" of Harlow in view of the secondary references to form immortalized B cell *ex vivo* by transfecting with an oncogene. Thus, there would be neither need nor motivation for the ordinarily skilled worker to employ an alternative approach and instead use the conditionally immortal cells of the transgenic Jat mouse.

Indeed, upon viewing Harlow, there is simply no evidence of a problem to be solved! Courts have long held that to render a claimed invention obvious, the prior art must recognize the source or existence of the problem in the first place. For example, the U.S. Supreme Court has

held that in the case of a known problem, the identification of the source of that problem is patentable, even where the solution is obvious once the source is known. *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45, 68 (1923). Similarly, a "patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified." *In re Sponnoble*, 160 U.S.P.Q. 237, 243 (C.C.P.A. 1969). A corollary to these principles is where the prior art fails to recognize the existence of a problem in the first place. In this regard, the CCPA has held that it is improper to conclude that an invention is obvious absent evidence that one of skill would have recognized that an underlying problem existed. *In re Nomiya*, 184 U.S.P.Q. 607 (CCPA 1975).

Claims 18 and 25-38

Claims 18 and 25-38 are directed to the use of transgenic antibody-producing cells that include *both* the ability to be immortalized (*e.g.*, that conditionally express a transforming oncogene) *and* the ability to produce human monoclonal antibodies. These embodiments are still further removed from the prior art. One example of such embodiments would be the use of a type of transgenic mouse that includes *both* the properties of a Xenomouse® and an Immortomouse® (see, in particular, claims 18 and 37). One of various ways to produce such a mouse is described in the specification at pages 15-17, particularly page 17, lines 6-8; "...a cross-bred mouse population (*e.g.*, Immortomouse®/Xenomouse® cross) may produce ...".

With respect to claims 25-38, we unable to find any reasoned explanation in the Action as to how the subject matter of such claims are obvious. The Action makes reference to Jat *et al.*, but the mice of Jat *et al.* produce *murine* antibodies, not human antibodies. Moreover, it is recognized that Kanki recites the immortalization of human primary B-lymphocytes, but the Action fails to explain how through the combination of Kanki with Jat *et al.* one could ever

arrive at a the invention of claims 25-38, directed to cells that *at the time* they are immuno-programmed they have both properties (*e.g.*, both *human* antibody-producing and capable of being immortalized through the *pre-existing* presence of an oncogene). Kanki alone certainly doesn't provide this ability, Jat *et al.* alone certainly doesn't provide this capability, and there is reasoned explanation of how combining these two references could arrive at such a capability. Moreover, claim 37 is directed to the use of *mouse* cells having *both* capabilities.

The Action fails to in any way even attempt to explain how the foregoing embodiments are rendered obvious.

With respect to claim 18, the Action adds in the reference of Green *et al.*, which simply describes the use of the Xenomouse® to produce human antibodies. But Green *et al.* fails to teach or suggest a means of providing a Xenomouse® that has antibody-producing cells comprising a pre-existing oncogene that renders them capable of being immortalized. To arrive at such a teaching one would be required to postulate, for example, the cross-breeding of the Xenomouse® with Immortomouse® -- yet, there is no such teaching or suggestion to be found that Applicants can discern, and the Examiner has neither pointed out such a suggestion nor reasonably attempted to explain how such a combination is obvious.

The Examiner apparently concedes this point in that Green is cited merely for the proposition that the Xenomouse could be used to produce human antibodies "due to the advantages related to clinical applications." Even then, though, the Action fails to identify any specific teaching within either Jat *et al.* or Green that would motivate the ordinarily skilled worker to cross the Green mouse with the Jat *et al.* mouse. The best the Action can do is to make the bald, unsupported statement that "[t]he skilled artisan would have readily recognized the need to interbreed the XENOMOUSE to the mouse of Jat in order to produce a mouse that

could produce human antibodies..." Action, page 5, para. 11. However, simply waiving hands and saying it is so, does not make it so. There is no reasoned basis identified by the Examiner for concluding that it would have been obvious to, for example, make such in interbred mouse.

Thus, for the foregoing reasons it is submitted that the Examiner has failed to set forth a *prima facie* case of obviousness and Applicants thus respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3055 is respectfully requested.

Respectfully submitted,

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